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Army research needs for automated neuropsychological tests: Monitoring soldier health and performance status☆

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Abstract

Information on the mental status of soldiers operating at the limits of human tolerance will be vital to their management in future deployments; it may also allow earlier intervention for conditions such as undiagnosed Gulf War illnesses and Parkinson's Disease. The Army needs a parsimonious set of neuropsychological tests that reliably identify subtle changes for: (1) early detection of individual health and military performance impairments and (2) management of occupational and deployment health risks. Testing must characterize cognitive lapses in healthy individuals faced with relevant operational stressors (i.e., anxiety, information overload, thermal strain, hypoxia, fatigue, head impact, chemical or radiation exposures, metabolic challenges). This effort must also explore the neuropsychological methods in militarily relevant conditions to extend our understanding of relevant functional domains and how well they correspond to modes of testing. The ultimate objective is unobtrusive real-time mental status monitoring.

Keywords: Neuropsychological testing; Neurophysiology; Military personnel; Neuroepidemiology; Health surveillance

1. Introduction

The soldier is the acknowledged centerpiece of the Army's warfighting system, and success largely depends on the mental status of these individuals. The complexity, speed, and lethality of modern warfare means that even small mental lapses may have catastrophic consequences. Judgment and other forms of decision-making, mood and cooperation, psychomotor performance, and cognitive status are all critical elements of soldier performance. In the military, these elements have been traditionally evaluated by observation or as net outcomes such as task or mission completion. Predictions of performance decrements produced by various environmental and occupational challenges have also been largely based on experience and observation. Thus, the absence of rigorously specified neuropsychological testing methods is a major technological barrier to advances in soldier performance research (Letz, 2003; White & Proctor, 1992). Investigation and prevention of soldier illnesses is also handicapped by this deficiency. Soldiers

☆ The opinions and assertions in this paper are those of the authors and do not necessarily reflect the official views of the Department of the Army or the Department of Veterans Affairs

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returning from the first Gulf War in 1991 reported unexplained and poorly defined neuropsychological symptoms; individuals evacuated from Iraq in 2005 with traumatic brain injury following concussive blast injuries still have no reliable assessment methodologies.

The development of the Automated Neuropsychological Assessment Metrics (ANAM) was started by Dr. Fred Hegge as a means to provide standardized and valid testing for a wide variety of military applications (Kabat, Kane, Jefferson, & DiPino, 2001; Kane & Kay, 1992). This came out of a 1984 program to assess the impact of operationally employed drugs on normal performance. These drugs included potential countermeasures against nerve agents which had become a high priority. Twenty years later, some of the same questions persist. In fact, a similar initiative to assess the impact of operationally employed drugs on performance was launched last year to address important concerns about effects of fatigue countermeasures (stimulant drugs) and an antimalarial drug (mefloquine) on soldier mood and judgment.

In May 2001, the Army sponsored a reunion in Pensacola of two dozen researchers who had piloted the development of neuropsychological tools under the sponsorship of Fred Hegge. During his tenure as the Director of the Office of Military Performance Assessment Technology (OMPAT) and later, as the Director of the Military Operational Medicine Research Program, Fred Hegge provided enthusiastic support to new and creative ideas. His leadership led to the development of novel approaches to assessment. However, we had reached a time where it was important to structure and consolidate gains and to impose some order on the chaotic mix of software versions and test procedures to enable comparisons of data between experiments. The Pensacola discussions recapitulated the lineage of ANAM from the Walter Reed Performance Assessment Battery that had first automated commonly used neuropsychological tests (Thorne, Genser, Sing, & Hegge, 1985). It concluded with current efforts to standardize the test procedures, software tools, and provide real-time analytic modules to facilitate use and interpretation. The wide diversity of applications discussed included assessment of the effects of stress faced by Navy divers, Marine recruits working in humid heat, work at altitude, fatigue, and exposure to toxic substances and radiation. These examples highlighted the need for a consistent and well developed approach to cognitive assessment. Unfortunately, only a few studies related to these stressors have been published as full reports in the open literature. Frequently, these studies were opportunistic and neither hypothesis driven nor part of a programmatic program of research. In some cases, the stressors were not well characterized. Even when ANAM was employed in military relevant research, testing methods varied between studies making comparisons across studies difficult. More recently, ANAM has been used to assess effects of injury and disease states (e.g., head injury, multiple sclerosis, and Parkinson's Disease). While different ANAM measures have been employed, there has been sufficient consistency to potentially shed light on anatomical and functional changes that can contribute to our understanding of less dramatic but important changes in healthy humans under stress. The thread that ties these issues together is the need of the military for a sensitive and consistent approach for measuring crucial changes in human performance.

The Pensacola summit kicked off a renewed effort by the Military Operational Medicine Research Program to develop a family of standardized ANAM tools and their applications through military studies, direct support to relevant extramural efforts, and leveraging of Congressional interest funding. The vision remains simple: we need better tools to practically test brain health and performance. This paper discusses the military research needs for ANAM test batteries in terms of anticipated applications and relevant neurophysiological studies.

2. Gulf war illnesses—a model of post-deployment neuropsychological concerns

Cognitive status changes important to soldier performance may also be important indicators of early disease changes. As a result of the 1991 Persian Gulf War neurological conditions acquired specific importance in research on soldier monitoring and protection. These range from chronic multi-symptom illnesses such as fibromyalgia, chronic fatigue syndrome, and multiple chemical sensitivities, to early indications of neurodegenerative diseases such as Parkinson's Disease (PD) and amyotrophic lateral sclerosis (ALS; Clauw, 2003; Horner et al., 2003). Seemingly every conceivable etiology has been proposed for undiagnosed Gulf War illnesses, but the investigations have narrowed to just a few factors, including soldier fitness and physical activity that may affect mental outlook and resilience (Glass et al., 2004), emotional stress influences (Clauw, 2003), and specific neurotoxicants (Proctor, 2000; Presidential Advisory Committee on Gulf War Veterans' Illnesses (PACGWVI), 1996; White, 2003). These concerns thrust neuropsychological testing into a central role in post-deployment health research.

Neuropsychological assessments of Gulf War veterans have been conducted in all of the major veteran study cohorts; unfortunately, only a few investigators have conducted rigorous testing and most have relied on symptom checklists. Every study has reported greater cognitive complaints for Gulf War veterans who deployed compared to non-deployed veterans, and nearly every study has described associated symptoms of fatigue and depression. For example, based on structured interviews, Iowa veterans who deployed to the Gulf had a higher prevalence of self-reported problems with memory and forgetfulness (>20% of respondents) compared to those who had not (6–8% of non-deployed respondents; Doebbling et al., 2000). There was a difference in the prevalence, but not in the nature of the complaints, with both deployed and non-deployed veterans reporting difficulty in concentrating and symptoms of depression. These and other studies indicate no unique syndrome or symptom complex, but a higher prevalence of illness in veterans who deployed to the Gulf, probably reflecting a general phenomenon affecting well-being of individuals after involvement in war or other significant events (Barohn & Rowland, 2002; Hyams, Wignall, & Roswell, 1996).

The subjective complaints are not well reflected in the neuropsychological testing performances. For example, Gulf War deployed veterans from Oregon and Washington states with undiagnosed illnesses revealed small differences in memory, attention, and response speed on a large battery of tests, but large differences in their psychological complaints compared to a sample of non-deployed (Storzbach, Campbell, Binder, et al. 2000). White et al. (2001) studied two cohorts of soldiers who deployed to the Gulf, and compared their responses to a group that was sent to Germany instead of the Gulf. Detailed testing revealed no statistically significant difference in cognitive functioning, but mood complaints were significantly higher in Gulf War-deployed. It was noted that soldiers who reported that they believed they had been exposed to chemical or biological warfare agents demonstrated poorer performance on several cognitive tests, raising issues about motivation (Lindem et al., 2003; White et al., 2001). Differences in cognitive test measures for Gulf War-deployed forces in the British studies disappeared after correction for multiple comparisons and adjustments for depressed mood (David et al., 2002). Proctor, White, Heeren et al. (2003) studied the entire cohort of Danish forces deployed just after the end of hostilities in the Gulf and found no differences in detailed neuropsychological testing compared to non-deployed personnel, but did find a higher incidence of mood complaints (fatigue and confusion). The most highly studied and reported sample is that of Robert Haley and his colleagues who have focused attention on two dozen sick veterans where intellectual and cognitive function were measurably decreased compared to a similar number of healthy veterans (Hom, Haley, & Kurt, 1997). Another study that includes detailed neuropsychological testing and objective brain biochemical changes evaluated by magnetic resonance spectroscopy is currently underway with veterans from northern California studied at the Veterans Administration Medical Center, San Francisco, by Dr. Michael Weiner; this study includes careful evaluation for depression, alcoholism, and post-traumatic stress disorder. These data from various Gulf War cohorts raise an important issue of the influence of mood disturbances on cognitive function testing. It remains an open question about how well these domains can be evaluated in an automated push-button test in patients with fatigue and depression. Future ANAM developments will almost certainly have to consider testing other sensory systems.

The emergence of chronic neurological symptoms and the proposed involvement of psychological or neurotoxicological causes opened the door to consideration of longer term neurological diseases, especially those with a suspected environmental influence such as ALS and Parkinson's Disease (PD). Although data supporting any connection between military service exposures and these diseases is very thin because of the small number of cases and long disease latency, we are still ill equipped to obtain early detection of disease in these individuals and test this connection. Neuropsychological testing is one approach being employed in the investigation of Gulf War illnesses and also in studies on early detection and monitoring disease progression in PD in Army-sponsored research. It remains to be seen if neuropsychological testing can provide a sensitive indication of neurodegenerative disease changes ahead of functional imaging and physiological testing (Camicioli, Grossmann, Spencer, Hudnell, & Anger, 2001).

3. Challenges to army applications

3.1. Baseline testing

In response to Gulf War Illnesses, deploying forces are now required to undergo pre- and post-deployment health status assessments. However, there is no practical method to establish baseline neuropsychological status of soldiers. The only information recorded that may help in the evaluation of future neuropsychological problems is a conventional medical history and self report information. A new attempt to collect more detailed health and psychological status

within the first week of military service, the Recruit Assessment Program (RAP), also provides only limited self-report questionnaire data (Hyams, Barrett, & Duque, 2002). A brief test battery is needed and may come out of a major study of soldiers pre- and post-deployment conducted by Vasterling, Proctor, Amoroso, Kane, and White (2006). A likely platform for such standardized testing and data repository would be the next version of a military-wide Comprehensive Health Care System II (now termed AHLTA) database (Riley, 2003). This would provide baseline measures for the individual, changes over time, comparison to every other tested soldier, and instant access to any qualified military health care provider.

3.2. Evaluation of new materiel

Materiel safety evaluations require a well standardized test methodology, and clearly demonstrated thresholds and definitions of impaired neuropsychological performance. This test capability is important for generation of valid test data to support approval of new drugs and other medical materiel (e.g., pesticides). In addition to FDA approvals for medical materiel products, the Army needs to test in operationally relevant environments to ensure that there are no important interactions between the product and key operational stressors. Therefore, a relevant test battery that provides valid data under poorly controlled field conditions is especially important. Neurobehavioral testing methods have been well developed for toxicological assessments (Anger, 1990; Anger, Otto, & Letz, 1996) and may provide a strong basis for field investigations of unforeseen interactions. Two neurotoxic exposures that have been repeatedly raised in connection with Gulf War Illnesses, the insecticide permethrin (used in soldier uniforms) and petroleum products are currently the focus of a NATO panel coordinating research to develop reliable assessment tools, including neuropsychological assessments. Non-medical products also require testing through the Army's process of new system evaluations (MANPRINT), which requires consideration of human factors and medical safety in the design of new equipment at all stages of the development process (Murnyak, Leggieri, & Roberts, 2003). Standardized neuropsychological testing could be an important tool for future MANPRINT evaluations.

3.3. Remote warfighter status monitoring

Soldiers may be out of sight of team members and leaders, operating in remote outposts, around walls in urban terrain, or fully encapsulated in protective clothing and masks. It could be critical to have objective information on the mental status of an individual or a team that cannot be more directly assessed. Ideally, the monitoring system would involve passive and continuous assessments. This is the concept behind Warfighter Physiological Status Monitoring (WPSM), a system of wear-and-forget non-invasive physiological monitors that will use a combination of sensor signals to determine how a soldier is doing, when the soldier has been injured, and when the soldier is headed for trouble in terms of injury consequences (e.g., overheating, dehydration, overexertion) or in terms of performance lapses (e.g., fatigue, psychological stress, information overload; Hoyt, Reifman, Coster, & Buller, 2002; Wittels, Johannes, Enne, Kirsch, & Gunga, 2002). The earliest form of a WPSM approach to neurocognitive assessments is likely to use extremes of the physiological range of measures such as very low or high blood glucose levels (from minimally invasive sub-dermal probes) and recent sleep history (from wrist-worn accelerometry) to predict likely performance lapses. Whatever system is employed will have to be developed against a reference standard of automated neuropsychological testing.

4. Operational stressors and test performance

4.1. Is there a common hierarchy of functional loss in healthy humans under stress?

Neuropsychological testing has been developed around diagnoses of specific functional losses from disease and serious brain injury. The application of these same tests to stress-induced decrements in performance in healthy individuals may not be appropriate. These decrements may not simply fall on the same continuum of generalized impairments produced by disease processes and it would be very unlikely that they reflect the same functional losses associated with specific brain lesions. On the other hand, if traumatic brain injury (e.g., from head impact), and common operational stressors follow a common hierarchical loss of function that begins with the loss of higher cortical functions involving mood and complex cognition, this has implications for the design of the parsimonious test battery. So, there are at least two distinct lines of testing research needed: (1) development of a simple Army-relevant test battery that

can assess stress-induced performance decrements, possibly in a generic approach that works across the common operational stressors, and (2) expansion or validation of the testing to provide neuropsychological baselines that are appropriate to later evaluation of serious head injury in battlefield casualties as well as early detection of neurological diseases including neurodegenerative disease.

Except for very specific brain disease lesions, there appears to be a general tendency for higher order functions to be lost first, if not in a specific sequence, suggesting that a few tests of complex behavior may suffice for the early and sensitive detection of neuropsychological status change. This is the case for hypoglycemia, with marked changes in cognitive testing occurring below 3 nmol/L; memory is one of the first tests affected (Frier, 2001). This is also the case with acute hypoxia, with an average 25% reduction in short-term memory during ascent from sea level to over 14,000 ft altitude, corresponding to a reduction from 96 to 40 torr in arterial partial pressure of oxygen (Fulco & Cymerman, 1988). Likewise, cold exposure (e.g., 1 h or more at 4 °C air, or immersed in water at 10 °C) produces reductions in memory more consistently and with greater sensitivity than any other neuropsychological test (Thomas, Ahlers, House, & Schrot, 1989; Thomas, Shurtleff, & Schrot, 1994). These three stressors appear to operate through separate mechanisms affecting brain function, yet produce the same impairments. Memory is one of the first functional axes affected, followed by tests in other domains such as attentiveness. This suggests that for some monitoring applications in healthy individuals, relatively simple test batteries could be devised that might provide a generalizable assessment of acute performance status.

Studies involving other stressors suggest greater specificity of functional impairments. Although head impact can be a focal insult affecting a specific region of the brain, concussion has generalized effects on the brain, and Warden et al. (2001) and Bleiberg et al. (2004) suggested that global speed of processing reflected in a simple reaction time might even provide a practical single test of impairment and return-to-duty status. Chronic psychological stress appears to produce specific functional deficits in a link between chronic cortisol exposure, shrinkage of the hippocampal volume, and effects on memory functions (Sapolski, 1996). Sleep deprivation and short-term interventions have been well studied by the military and the neuropsychological impairments are associated with regional hypometabolic responses in the brain. Memory tests are not very sensitive to the effects of fatigue, especially compared to tests of attentiveness such as the psychomotor vigilance test (PVT; Balkin et al., 2004). Regardless of the stressor, there appears to be a common behavioral strategy to handle impairments. In a variety of tests that include hypoglycemia, concussion, and sleep deprivation, the overall speed of mental processing is typically sacrificed to preserve accuracy (Bleiberg et al., 2004; Frier, 2001; Penetar et al., 1994); thus, speed of processing might be a productive common measurement.

4.2. *Influence of mood state on testing variables*

Neuropsychological testing relevant to military applications is most advanced in the area of neurotoxicology (Anger, 1990; Anger et al., 1996; Fiedler, 1996; White & Proctor, 1997). Various classes of chemicals have been characterized for their highly specific regional and functional effects. In some cases, neuropsychological effects of heavy metals, solvents, organophosphates, and various agricultural and industrial chemicals provide the primary classification of biological effects, where physiological and anatomical lesions may be much more difficult to measure. ANAM testing methods could be further advanced with validation against the better-established neurotoxicology models (Proctor, Letz, & White, 2000). Current Army initiatives include testing effects of permethrin and JP8, following up on other human and animal studies demonstrating neurocognitive deficits (Tu, Mitchell, Kay, & Risby, 2004; McDaniel & Moser, 1993). Mood changes are among the first and most consistent changes with neurotoxicants. The influence of mood state and other additional psychological and environmental stressors on neurotoxicological responses in a military deployment needs to be carefully studied to make practical field tools useful. Neuropsychological testing in experimental settings is likewise affected by subjects temporarily rallying to complete a test even when they may be extremely fatigued or challenged in some other way.

Mood disturbances including increased irritability and depression are prevalent in many of these stressors including, for example, hypoxia (Fulco & Cymerman, 1988), neuroglycopenia (Frier, 2001), and a variety of neurotoxicants (White & Proctor, 1997). At present, the subjective Profile of Mood States (McNair, Lorr, & Droppleman, 1971) is the primary instrument in assessing current mood state; alternate tests that objectively quantify and distinguish characteristics such as curtness, lassitude, and helplessness from timed responses that also attempt to measure cognitive lapses in speed or accuracy have not yet been produced. Advances in methods to assess mood will be invaluable in neuropsychological evaluations.

4.3. Management of data and/or decision on test outputs

Researchers are drowning in the large volume of data produced by neuropsychological test batteries, with the large number of test options, variations in how the tests are administered, and more outcome variables such as speed and accuracy associated with each test. This seemingly infinite combination of outcome measures complicates interpretation of results, comparability to other studies, and study design because of the increased likelihood of Type II error. If many of the available tests truly represent different functional axes, then new bioinfomatic methods may be needed to interpret data. Alternatively, the testing could be reduced to five or six key tests with some kind of consensus standard. As an example, Kabat et al. (2001) found commonalities in some of the ANAM tests using principal components analyses, identifying three factors: processing speed/efficiency, retention/memory, and working memory. Bleiberg, Kane, Reeves, Garmoe, and Halpern (2000) produced similar factors in a separate analysis of data sets from sports concussion studies. Conceivably, one test with the strongest weighting against each factor could be selected as the starting point for an efficient test battery. The ANAM Readiness Evaluation System (ARES) battery devised by Reeves and Elsmore to operate on a PDA is an example of a parsimonious starting point with standard batteries consisting of 3,7, and 9 test measures. This test system is described in another paper in this collection (Elsmore, Reeves and Reeves, 2005).

5. Future possibilities

Future neuropsychological assessments may be used in machine decision algorithms to avert catastrophic failures. The future soldier will be an extraordinarily powerful and lethal system, and decision-making ability of the human element will be of critical importance. Commanders may rely on monitoring systems to indicate when soldiers are incapacitated and when human failure is imminent. Reliability of the mental status assessments will be especially important in any applications where the system can automatically take control away from the human in the loop. This concept of machine decision assist is the basis of several current DoD programs that range from balancing workload and decision making between team members based on the cognitive status assessment of each individual to systems that would take away controls of an aircraft if the pilot appears to be impaired, either through physiological measurements or illogical responses (Forster, Morrison, Hitchcock, & Scerbo, 1994). Future soldier concepts include technologically enabled individuals operating in teams with unprecedented access to information, decision aids, multi-sensory inputs ranging from tactile feedback to 3-D audio spatial “displays,” and instant fingertip or voice access to unmanned aerial vehicles and other remote robotic weapons and intelligence systems, and other equipment and adornments. The new technologies add to the neuropsychological burden of the soldier, but also provide more opportunities to unobtrusively monitor performance status through physiological measures or through embedded performance testing. Neuropsychological training to build cognitive resilience and specific skills could also be developed with reinforcement through adaptive testing and gaming routines that take advantage of brain neuroplasticity. New initiatives on topics such as neurobiology of exercise are also likely to provide enhancements of innate neuroprotection that will be tested and measured with neuropsychological tools.

6. Conclusion

The diverse military applications of ANAM testing described in this paper represent an ambitious agenda, but this does not imply that a single test battery or methodology is an appropriate fit to all these purposes. ANAM is intended to provide a family of standardized tests that can be translated across platforms, with batteries tailored to the appropriate use. Interpretation of test results will also vary according to the intended application, with very different standards and thresholds applied to epidemiological health screening tools and to individual fitness-for-duty tests. A very important part of this effort is to explore the neuropsychological methods in militarily relevant conditions to extend our understanding of relevant functional domains and how well they correspond to modes of testing. The first proof of the value of the ANAM investment is the application of an ANAM test battery with a reputation as a practical standard of testing and proven predictive or diagnostic value.

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